REVIEW

Artificial and Bioartificial Support Systems for Acute and Acute-on-Chronic Liver Failure

A Systematic Review

Lise L. Kjaergard, MD
Jianping Liu, PhD
Bodil Als-Nielsen, MD
Christian Gluud, DMSc

Context Artificial and bioartificial support systems may provide a "bridge" for patients with severe liver disease to recovery or transplantation.

Objective To evaluate the effect of artificial and bioartificial support systems for acute and acute-on-chronic liver failure.

Data Sources Randomized trials on any support system vs standard medical therapy were included irrespective of publication status or language. Nonrandomized studies were included in explorative analyses. Trials were identified through electronic searches (Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Library, MEDLINE, EMBASE, and the Chinese Medical Database), bibliographies, and contact with experts. Searches were conducted of the entire databases through September 2002.

Study Selection Of 528 references identified, 12 randomized trials with 483 patients were included. Eight nonrandomized studies were included in explorative analyses.

Data Extraction Data were extracted and trial quality was assessed independently by 3 reviewers (L.L.K., J.L., B.A-N.). The primary outcome measure was all-cause mortality. Results were combined on the risk ratio (RR) scale. Random-effects models were used. Sources of heterogeneity were explored through meta-regression and stratified meta-analyses.

Data Synthesis Of the 12 trials included, 10 assessed artificial systems for acute or acute-on-chronic liver failure and 2 assessed bioartificial systems for acute liver failure. Overall, support systems had no significant effect on mortality compared with standard medical therapy (RR, 0.86; 95% confidence interval [CI], 0.65-1.12). Meta-regression indicated that the effect of support systems depended on the type of liver failure ($P = .03$). In stratified meta-analyses, support systems appeared to reduce mortality by 33% in acute-on-chronic liver failure (RR, 0.67; 95% CI, 0.51-0.90), but not in acute liver failure (RR, 0.95; 95% CI, 0.71-1.29). Compared with randomized trials, nonrandomized studies produced significantly larger estimates of intervention effects ($P = .01$).

Conclusion This review suggests that artificial support systems reduce mortality in acute-on-chronic liver failure compared with standard medical therapy. Artificial and bioartificial support systems did not appear to affect mortality in acute liver failure.

JAMA. 2003;289:217-222 www.jama.com

LIVER FAILURE IS CHARACTERized by hepatic encephalopathy, jaundice, coagulopathy, and high mortality rates.[1,2] Viral hepatitis, drugs, or toxins can precipitate acute liver failure in patients without chronic liver disease.[3,4] Metabolic stress such as bleeding or infections can precipitate acute-on-chronic liver failure in patients with chronic liver disease.[5] Liver transplantation cures approximately 90% of patients with liver failure,[6,7] but there is a serious shortfall of donors and costs are considerable.[8] Furthermore, some patients may recover spontaneously without liver transplantation.[3]

The objective of artificial and bioartificial support systems is to "bridge" patients with liver failure to transplantation or recovery. Liver support must include removal of toxins, synthesis of products, and treatment of inflammation.[1] The first artificial support systems removed toxins through hemodialysis, hemofiltration, or hemoperfusion.[1,2,7] More recent systems combine hemodialysis with adsorption to charcoal or albumin (hemodiabsorption)[9,10] or use living hepatocytes, which add synthetic functions to the detoxification (bioartificial support systems).[11,12]

We performed a systematic review to evaluate the effect of artificial and bioartificial liver support systems for acute and acute-on-chronic liver failure. The primary analyses were based on randomized trials. Nonrandomized studies[13] were included in explorative analyses.[14]

Author Affiliations: The Cochrane Hepato-Biliary Group, The Copenhagen Trial Unit, Centre for Clinical Intervention Research, H:S Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark (Drs Kjaergard, Liu, Als-Nielsen, and Gluud), and West China Hospital, Sichuan University, Chengdu, Sichuan, China (Dr Liu).

Corresponding Author and Reprints: Lise L. Kjaergard, MD, The Cochrane Hepato-Biliary Group, The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, H:S Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark (e-mail: kjaergard@ctu.rh.dk).

METHODS

Literature Search and Eligibility Criteria

The review was performed according to a published protocol.[15,16] Three reviewers participated in the literature searches, selection of trials, and data extraction. We included randomized trials comparing any support system vs standard medical therapy for acute or acute-on-chronic liver failure irrespective of publication status or language. Quasi-randomized and nonrandomized studies were evaluated in explorative analyses. Eligible trials were identified through Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Library, MEDLINE, EMBASE, and the Chinese Medical Database. Included terms were *liver*, *artificial*, or *liver failure,* and (*rand* or controlled*). We also screened bibliographies of relevant articles and conference proceedings and wrote experts. The searches were performed of the entire databases through September 2002.

Data Extraction and Outcome Definition

For each trial, we gathered data on the following characteristics: type of liver failure (acute or acute-on-chronic), mean age, proportion of men, type of support system, trial quality, setting, duration of follow-up, and losses to follow-up. Data were sought on all patients irrespective of compliance or follow-up. Disagreements were resolved through consensus. Primary investigators were contacted if data were incomplete.

All outcomes were assessed at maximum follow-up. The primary outcome measure was all-cause mortality. Secondary outcome measures were bridging to liver transplantation (number of patients who were too ill to receive a liver transplantation), hepatic encephalopathy (number of patients without improvement of mental state), and adverse events.[17]

Assessment of Methodological Quality and Statistical Analysis

Three reviewers (L.L.K., J.L, B.A-N.) independently assessed trial quality[18-20] by examining the allocation sequence generation, allocation concealment, and blinding of outcome assessors. The allocation sequence generation was classified as adequate if based on computer-generated random numbers, table of random numbers, or similar.[20] The allocation concealment was classified as adequate if the allocation sequence was concealed until the moment of randomization by a central independent unit, sealed envelopes, or similar.[20]

Results of individual trials were combined on the risk ratio (RR) scale. Random effects models were used. Inter-trial heterogeneity was estimated by χ^2 tests. All patients were included in the analyses irrespective of follow-up (intention-to-treat). If outcome data were missing, we used carry forward of the last-observed response. The extent to which the patient, intervention, and trial characteristics could explain heterogeneity was explored through simple random effects meta-regression. The outcome was mortality (log RR). Weights were assigned according to the estimated variance (SEs to the log RR). The following covariates were entered: type of liver failure, mean age, proportion of men, year of publication, type of support system, quality, and publication status. If the meta-regression indicated a significant association between covariates and intervention effects, RR and 95% confidence interval (CI) were calculated in stratified meta-analysis. The risk of bias was explored through statistical testing of funnel plot asymmetry.[21] Explorative meta-regression analyses including nonrandomized studies were also performed.

In a post hoc sensitivity analysis, we recalculated our primary meta-analysis without 1 trial[22] published several years before the remaining trials. We also performed a post hoc worst case scenario analysis in which patients with missing outcome data were considered as treatment failures. Analyses were performed with STATA version 6.0 (Stata Corp, College Station, Tex) and Review Manager version 4.0 (RevMan, The Cochrane Collaboration, Oxford, England). $P<.05$ was considered statistically significant.

RESULTS

Identification of Eligible Trials

After screening 528 references, we excluded 473, because they were duplicates, nonclinical, or clearly irrelevant. Of the remaining 55 references, 32 were excluded because they did not meet our inclusion criteria. Three ongoing trials could not be included because data were unavailable. Eight nonrandomized studies[23-30] were excluded from the primary analyses, but were included in explorative analyses. Twelve randomized trials on artificial or bioartificial support systems vs standard medical therapy were included in the primary analyses (TABLE 1).[9,11,12,22,31-38]

Characteristics of Patients and Interventions

The 12 trials included 483 patients with acute liver failure (n=353, 73%) or acute-on-chronic liver failure (n=130, 27%). Eleven trials reported the mean age of included patients (range, 26-53 years) and the proportion of men (range, 33%-87%). All trials were performed in intensive care units.

Ten of the included trials evaluated artificial systems (Table 1). Five trials[9,32-35] assessed the BioLogic-DT (HemoCleanse Inc, West Lafayette, Ind) system, which is based on hemodiabsorption with powdered-activate charcoal. Two trials[36,38] assessed the molecular adsorbent recirculating system, which is based on hemodiabsorption with albumin. The remaining artificial systems were whole-blood exchange,[22] charcoal hemoperfusion,[31] and plasma exchange with hemoperfusion.[37] Two trials assessed bioartificial systems based on human liver-derived tumor cells (the extracorporeal liver assist device),[11] or porcine hepatocytes (the HepatAssist device).[12] In all trials, the control groups received standard medical therapy for complications associated with severe liver failure, including electrolyte substitution, fluid substitution, antacid therapy, coagulation therapy, and *N*-acetylcysteine.

Follow-up of Included Patients

In 2 trials, the primary outcome was 30-day survival.[36,38] In the remaining trials, follow-up was estimated by the reported survival data. Overall, the median duration of follow-up was 28 days (range, 0-33 days). Of the 244 patients randomized to support systems, 7 died before treatment and 2 were withdrawn due to adverse events (Table 1). Of the 239 patients randomized to standard medical therapy, 1 patient died before treatment and 1 patient received a liver transplantation before treatment. In 1 trial,[33] data were missing on 4 patients randomized to standard medical therapy.

Methodological Quality and Publication Status of Included Trials

The allocation sequence generation was adequate in 5 trials[11,31,34,36,38] and the allocation concealment was adequate in 9 trials.[9,11,22,32-36,38] Only 1 trial reported blinded-outcome assessment.[38] Two trials were published as abstracts.[12,33] One trial was unpublished when we completed our review, but has been published as a full article.[38] The remaining trials were published as full articles.

Statistical testing of funnel plot asymmetry revealed no evidence of bias ($P=.50$). The sensitivity analyses and meta-regression did not identify significant associations between randomization ($P=.96$) or publication status ($P=.22$) and intervention effects.

Effects on Mortality

Mortality was reported in all 12 trials. The control group mortality rate was 51% (123/239). Overall, support systems did not appear to reduce mortality significantly compared with standard medical therapy (RR, 0.86; 95% CI, 0.65-1.12). The intertrial heterogeneity was significant in this analysis ($P=.04$). In meta-regression analysis, there was evidence of a significant association between the effect of support systems and the type of liver failure ($P=.03$). In a stratified meta-analysis, artificial support systems seemed to reduce mortality by 33% in acute-on-chronic liver failure (TABLE 2). Artificial and bioartificial support systems did not seem to have a significant effect on mortality in acute liver failure. In these analyses, intertrial heterogeneity was not statistically significant ($P=.43$ and $P=.15$, respectively).

The meta-regression analyses showed little evidence of an association between the effect of support systems on mortality and the following covariates: type of support system ($P=.10$), publication year ($P=.20$), mean age ($P=.06$), or proportion of men ($P=.58$).

In a post hoc sensitivity analysis, we recalculated the primary meta-analysis without 1 trial,[22] which was published in 1973. After exclusion of this trial, the effect of support systems on mortality approached statistical significance (RR, 0.78; 95% CI, 0.61-1.00). The intertrial heterogeneity was not statistically significant ($P=.20$). We also performed a post hoc worst case scenario analysis in which patients with missing outcome data were considered as treatment failures. In this analysis, support systems did not seem to have a significant effect on mortality (RR, 0.82; 95% CI, 0.62-1.08). The intertrial heterogeneity was statistically significant ($P=.02$).

Table 1. Characteristics of 12 Randomized Trials on Artificial and Bioartificial Support Systems for Liver Failure

			Intervention Group		Control Group	
Source	Intervention	Type of Liver Failure	Sample Size	Losses to Follow-up	Sample Size	Losses to Follow-up
		Artificial Systems				
Redeker and Yamahori,[22] 1973	Whole-blood exchange	Acute	15	7 Died before treatment	13	None described
O'Grady et al,[31] 1988	Charcoal hemoperfusion	Acute	29	None described	33	None described
Hughes et al,[32] 1994	BioLogic-DT	Acute	5	None described	5	None described
Mazariegos et al,[33] 1997	BioLogic-DT	Acute	5	None described	5	Data missing on 4 patients
Kramer et al,[34] 1998	BioLogic-DT	Acute-on-chronic	10	None described	10	None described
Ellis et al,[35] 1999	BioLogic-DT	Acute-on-chronic	5	None described	5	None described
Mitzner et al,[36] 2001	MARS	Acute-on-chronic	8	None described	5	None described
Heemann et al,[38] 2002	MARS	Acute-on-chronic	12	None described	12	1 Died before treatment
Wilkinson et al,[9] 1998	BioLogic-DT	Acute/acute-on-chronic	6	None described	5	1 Received transplant before treatment
He et al,[37] 2000	Hemoperfusion	Acute/acute-on-chronic	64	None described	60	None described
		Bioartificial Systems				
Ellis et al,[11] 1996	ELAD	Acute	12	2 Withdrawn (adverse events)	12	None described
Stevens et al,[12] 2001	HepatAssist device	Acute	73	None described	74	None described
Total			**244**		**239**	

Abbreviations: ELAD, extracorporeal liver assist device; MARS, molecular adsorbent recirculating system.

Table 2. Effect of Artificial and Bioartificial Support Systems on Mortality in Acute and Acute-on-Chronic Liver Failure*

Source	No. of Events/ No. of Patients		Weight, %	Risk Ratio (95% Confidence Interval)
	Intervention	Control		
Acute Liver Failure				
Redeker and Yamahori,[22] 1973	14/15	9/13	24.6	1.35 (0.92-1.98)
O'Grady et al,[31] 1988	19/29	20/33	24.9	1.08 (0.74-1.58)
Hughes et al,[32] 1994	4/5	2/5	5.8	2.00 (0.63-6.38)
Ellis et al,[11] 1996	4/12	5/12	7.0	0.80 (0.28-2.27)
Mazariegos et al,[33] 1997	1/5	1/5	1.4	1.00 (0.08-11.93)
Wilkinson et al,[9] 1998	0/1	1/2	1.3	0.50 (0.04-7.10)
He et al,[37] 2000	10/37	15/33	14.2	0.59 (0.31-1.14)
Stevens et al,[12] 2001	20/73	30/74	20.9	0.68 (0.42-1.08)
Total	**72/177**	**83/177**	**100**	0.95 (0.71-1.29)
Acute-on-Chronic Liver Failure				
Kramer et al,[34] 1998	4/10	4/10	7.0	1.00 (0.34-2.93)
Wilkinson et al,[9] 1998	3/5	3/3	15.7	0.60 (0.39-1.23)
Ellis et al,[35] 1999	5/5	5/5	0	NA
Mitzner et al,[36] 2001	6/8	5/5	50.4	0.75 (0.50-1.12)
He et al,[37] 2000	10/27	17/27	24.8	0.59 (0.33-1.04)
Heemann et al,[38] 2002	1/12	6/12	2.1	0.17 (0.02-1.18)
Total	**29/67**	**40/62**	**100**	0.67 (0.51-0.90)

Abbreviation: NA, not applicable.
*Because of rounding, percentages may not all total 100. Weights were assigned according to the estimated variance (SEs to the log risk ratio).

Table 3. Risk Ratios for Bridging to Transplantation and Hepatic Encephalopathy, and Type of Adverse Events in 12 Randomized Trials on Support Systems vs Standard Medical Therapy

Source	Risk Ratio (95% Confidence Interval)		Type of Adverse Events in Intervention Group†
	Bridging to Transplantation*	Hepatic Encephalopathy*	
Redeker and Yamahori,[22] 1973	Not assessed	Not assessed	None reported
O'Grady et al,[31] 1988	1.00 (0.57-1.76)	Not assessed	None reported
Hughes et al,[32] 1994	Not assessed	1.00 (0.36-2.75)	None reported
Ellis et al,[11] 1996	Not assessed	0.25 (0.03-1.92)	Bleeding, coagulopathy, hypotension, fever, hypersensitivity
Mazariegos et al,[33] 1997	0.60 (0.29-1.23)	0.60 (0.29-1.23)	Bleeding
Kramer et al,[34] 1998	0.90 (0.73-1.11)	1.00 (0.56-1.78)	Bleeding, coagulopathy, disseminated intravascular coagulation
Wilkinson et al,[9] 1998	0.62 (0.25-1.56)	0.67 (0.38-1.17)	Coagulopathy
Ellis et al,[35] 1999	Not assessed	0.50 (0.16-1.59)	None reported
He et al,[37] 2000	Not assessed	0.59 (0.38-0.90)	Bleeding, sepsis, allergic shock, hypersensitivity, arrhythmia, electrolyte imbalances
Mitzner et al,[36] 2001	Not assessed	Not assessed	Coagulopathy (low platelet count)
Stevens et al,[12] 2001	Not assessed	Not assessed	Coagulopathy, hypotension, sepsis, renal failure
Heemann et al,[38] 2002	Not assessed	0.14 (0.01-2.50)	Bleeding, coagulopathy, hypotension, fever, anemia
Overall	0.87 (0.73-1.05)	0.67 (0.52-0.86)	

*Number of patients who were too ill to receive liver transplantation.
†Reported adverse events in intervention group. The occurrence of adverse events in the control groups in individual trials was incompletely reported and no meta-analysis was performed.

Effects on Liver Transplantation and Hepatic Encephalopathy

We were able to extract data on bridging to liver transplantation from 4 trials[9,31,33,34] and hepatic encephalopathy from 8 trials.[9,11,32-35,37,38] Meta-analyses of these data indicated that support systems had no significant effect on bridging to liver transplantation (RR, 0.87; 95% CI, 0.73-1.05) but a significant positive effect on hepatic encephalopathy (RR, 0.67; 95% CI, 0.52-0.86) (TABLE 3). In these analyses, intertrial heterogeneity was not statistically significant ($P = .54$ and $P = .57$, respectively).

Adverse Events

Support systems were associated with several serious and nonserious adverse events (Table 3). The registration of adverse events associated with standard medical therapy was incomplete and we were therefore unable to perform a reliable meta-analysis of this outcome. The most important adverse event appeared to be bleeding, which was registered as serious in 3 trials[11,33,34] and nonserious in 2 trials.[37,38] Other serious adverse events included disseminated intravascular coagulation, allergic shock, fever, sepsis, hypotension, and renal failure. Eight trials reported that support systems were associated with coagulopathy because of a decrease in platelet counts or antithrombin III levels.[9,11,12,33,34,36-38] Other nonserious adverse events included hypersensitivity, electrolyte disturbances, and anemia.

Nonrandomized Studies

We performed explorative analyses in which 8 nonrandomized studies were included.[23-30] Three were case series with historical controls and assessed artificial support systems for acute liver failure.[23,25,26] Five studies were prospective with contemporary controls.[24,27-30] These studies assessed bioartificial[24] or artificial systems[27-30] and included patients with acute[24,28] or acute-on-chronic liver failure.[27,29,30]

A meta-regression analysis indicated that the estimated effect of support systems on mortality was significantly dif-

ferent in randomized trials and nonrandomized studies ($P=.01$). In randomized trials, 123 of 239 patients (51%) allocated to the control group died compared with 130 of 204 patients (64%) in studies with contemporary controls and 222 of 262 patients (85%) in studies with historical controls. Accordingly, the method of allocation (randomized or nonrandomized) was associated with control group event rates ($P=.001$). Support systems did not have a significant effect on mortality in randomized trials (RR, 0.86; 95% CI, 0.65-1.12) but appeared to reduce mortality significantly in studies with contemporary (RR, 0.72; 95% CI, 0.55-0.95) or historical controls (RR, 0.68; 95% CI, 0.58-0.80).

COMMENT

This review of 12 randomized trials compared the effect of artificial and bioartificial support systems with standard medical therapy for severe liver failure. In the primary meta-analysis, support systems did not appear to affect mortality. However, there was significant intertrial heterogeneity and meta-regression analyses indicated that the effect of support systems was associated with the type of liver failure. In a stratified meta-analysis, artificial support systems reduced mortality by 33% in acute-on-chronic liver failure. None of the identified randomized trials assessed the effect of bioartificial support systems for acute-on-chronic liver failure. Artificial and bioartificial support systems did not appear to reduce mortality in acute liver failure. However, these subgroup analyses can only be considered as hypothesis generating. Although the evidence seems promising, additional randomized trials are needed before support systems can be recommended for routine use.

The included trials were performed at specialized intensive care units. Transport to these units may be an additional hazard to patients with severe liver disease. This aspect cannot be answered by this review, but should be included in the overall assessment of intervention benefits. Another question is whether the intervention is associated with long-term benefits. Most of the included patients were followed up for about 1 month. However, the primary purpose of support systems is to bridge patients with severe liver failure to liver transplantation or recovery. Short-term follow-up is therefore important.

Mortality in severe liver failure depends on the degree of liver damage and regenerative ability. Support systems may provide a bridge during treatment of bleeding or infections, which are the most common causes of acute-on-chronic liver failure. Precipitating factors in acute liver failure include drug toxicity and viral hepatitis, which are difficult to treat. This may explain why our analyses indicated that support systems are effective in acute-on-chronic but not in acute liver failure.

We observed a positive effect of support systems on hepatic encephalopathy but not on bridging to liver transplantation. Support systems seemed to be associated with several potentially life-threatening adverse events. The most frequently reported were bleeding and infections. However, the included patients had severe liver disease, and it may be difficult to estimate whether the treatment or the underlying disease caused the adverse events. Due to incomplete reporting, we were unable to perform a reliable analysis of the occurrence of adverse events. We were also unable to assess the effect on quality-of-life and health economics. Additional evidence addressing these issues is warranted.

Limitations

This review has potential limitations. Meta-analyses are by nature observational and may therefore be affected by bias or confounding. We performed a limited number of predefined subgroup analyses. The results of these analyses should be interpreted with caution and prospective validation is needed before causal inferences can be made. Furthermore, the event rates and number of included patients indicate that our primary meta-analysis had less than 40% power of detecting a 10% reduction in mortality, possibly making our conclusions false negative.

We attempted to avoid publication bias by thorough literature searches. We found no statistically significant evidence of bias. However, the individual trials were relatively small and may therefore have generated false-negative or false-positive conclusions due to random error.[39] Only 1 trial reported preset sample size calculations.[38] In the remaining trials, we were unable to determine whether the preset sample size was reached or whether it was terminated at an arbitrary time.

Due to the nature of support systems, adequate double blinding of patients and caregivers was impossible. Blinded outcome assessment could be performed but was only used in 1 trial.[38] Improvement of hepatic encephalopathy is a soft outcome measure that may be influenced by the convictions of the assessor. Lack of blinding increases the risk of false-positive conclusions about this outcome.[18-20]

Interim analyses have a considerable risk of generating false-positive results and require very small significance levels before a trial is stopped.[40-42] One generally accepted method for assessing interim analyses[40] specifies that the significance level should be less than $P \leq .001$. One of the included trials was prematurely stopped after an interim analysis, which indicated a significant intervention benefit.[38] However, the statistical significance of the interim analysis was only 3% and the decision to terminate the trial is therefore debatable.

Nonrandomized studies may have greater external validity if patients who are willing to enter a randomized trial differ from patients who are not.[13,14] However, the question of external validity becomes irrelevant if the internal validity is questionable. If prognostic factors are unevenly distributed in the experimental and control groups, it is impossible to determine whether differences reflect the intervention or baseline prognosis.[43] We found that control group event rates were higher and intervention effects more positive in nonrandomized studies compared with randomized trials. These findings concur with previous evidence,

which indicate that nonrandomized studies have a considerable risk of generating false-positive conclusions.[43]

Implications

The present review indicates that patients with acute-on-chronic liver failure may benefit from treatment with artificial liver support systems. The evidence concerning bioartificial support systems and treatment of patients with acute liver failure was less conclusive. However, randomized trials on artificial or bioartificial support systems vs standard medical therapy for acute and acute-on-chronic liver failure still seem justified.

Author Contributions: *Study concept and design:* Kjaergard, Liu, Als-Nielsen, Gluud.
Acquisition of data: Kjaergard, Liu, Als-Nielsen.
Analysis and interpretation of data: Kjaergard, Liu, Als-Nielsen, Gluud.
Drafting of the manuscript: Kjaergard.
Critical revision of the manuscript for important intellectual content: Liu, Als-Nielsen, Gluud.
Statistical expertise: Kjaergard, Liu, Als-Nielsen, Gluud.
Obtained funding: Gluud.
Study supervision: Liu, Gluud.
Funding/Support: This work was funded by The Danish Medical Research Council, The 1991 Pharmacy Foundation, Denmark, The Copenhagen Hospital Corporation Medical Research Council, and Danish Centre for Evaluation and Health Technology Assessment (DACEHTA).
Acknowledgment: We thank the authors who provided additional data on their trials. We also thank Wendong Chen, MD, for validating the data extraction of Chinese trials.

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